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Estimating the glomerular filtration rate in pregnancy: The evaluation of the Nanra and CKD-EPI serum creatinine-based equations

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Abstract

Aim: To compare the performance of the Nanra and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating glomerular filtration rate in pregnancy against the 24 h urine creatinine clearance.

Methods: Pregnant women had 24 h urine collections with simultaneous serum creatinine levels. Measured 24 h urine creatinine clearance was compared to two equations: Nanra and CKD-EPI. Level of concordance was measured, with an *a priori* bias acceptance of $\pm$15 ml/min/1.73 m^2.

Results: A total of 53 synchronous urine and serum creatinine samples were analysed. The Nanra equation had a bias of $-$13.4 ml/min/1.73 m^2 while the CKD-EPI equation had bias of 14.2 ml/min/1.73 m^2. Both equations showed a high degree of proportional error and had poor agreement with 24 h urine creatinine clearance.

Conclusions: None of the equations were shown to reliably measure the estimated glomerular filtration rate in pregnant women. A valid serum creatinine-based estimated glomerular filtration rate equation in pregnancy is yet to be established.

Keywords

Glomerular filtration rate, pregnancy, serum creatinine, creatinine clearance, Nanra, CKD-EPI

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Background

Renal impairment during pregnancy is associated with increased maternal and fetal risk.[1,2] Women with pre-existing renal disease have a higher incidence of progressive kidney damage during pregnancy.[3] Moreover, conditions such as pre-eclampsia can cause new onset renal impairment during pregnancy itself. With these women at higher risk of pregnancy-related complications and neonatal morbidity, the identification and monitoring of renal impairment is an important step in reducing the rate of adverse events.[4] Currently the only practical and validated method to measure renal function in pregnancy is the 24 h urine creatinine clearance, a complicated and often impractical task. This stresses the need for an accurate and practical measure of kidney function in pregnancy.

The gold standard measure of renal function using inulin clearance is unsuitable in clinical practice and is rarely used outside of scientific studies. Isotopic glomerular filtration rate (GFR) measurements should also be avoided in pregnancy due to the potential fetal risks associated with the use of a radioactive isotope. Current recommendations advise the use of 24 h urine creatinine clearance to measure renal function in pregnancy; however, this is often challenging and may be incomplete due to practical difficulties.[4–6] This means that often the trend in serum creatinine is monitored instead in a high-risk pregnancy. Serum creatinine is variable due to an increase in GFR during adaptive hyperfiltration at different stages of pregnancy, though the trend can be monitored and results beyond the 95th percentile thresholds suggest renal impairment.[7] However, it is well known that the serum creatinine is affected by muscle mass and other nutritional factors which make it less reliable for assessing renal function. Formulas used in the adult population, such as the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) equation, are inaccurate in the pregnant population.[5,6,8]

A new estimated creatinine clearance formula, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, was recommended by the Australasian Creatinine Consensus Working Group in 2012. Compared to the MDRD equation it has improved precision in healthy adults when the GFR is over 60 ml/min.[9] Due to

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the adaptive physiological increase in renal function during pregnancy, CKD-EPI equation is a theoretically more accurate measure of GFR.[4] Despite this, some studies have shown poor concordance between the CKD-EPI equation and validated measures of renal function in pregnancy.[10,11]

The Nanra equation, named after its creator, has been validated in some populations to estimate GFR, such as renal transplant patients, but not in pregnancy.[12] This equation takes height into consideration rather than weight, which will theoretically allow a more accurate estimation of GFR in pregnancy where individual weight is altered by the pregnancy.

With pregnancy-related weight gain and body surface area (BSA) changes not being representative of an increase in serum creatinine production, we hypothesise that the Nanra equation will provide better estimations of GFR in the pregnant population. The aim of this study is to compare the GFR obtained from the 24 h urine creatinine clearance to the CKD-EPI and Nanra equations. Achieving a valid estimated GFR in pregnancy would alleviate the need for 24 h urine collections and allow for a practical, cheaper and less error-prone measure of renal function.

Methods

Pregnant women who were over 12 weeks of gestation were prospectively recruited after written consent from the low risk antenatal outpatient clinic at John Hunter Hospital, Newcastle, between 2016 and 2017. The study was approved by the local ethics committee. Women were excluded if they had diabetes, renal disease, single kidney, or hypertension. One to two 24 h urine collections were obtained from each participant at different stages of their pregnancy prior to 36 weeks of gestation. Each woman had their gestational age, height, weight and blood pressure measured at the time of their 24 h urine collection, and a simultaneous serum creatinine level was taken. Participants were provided with written instructions regarding their 24 h urine collection to avoid inaccuracies. All laboratory tests were performed in one pathology laboratory to avoid inter-laboratory variation in assays. Serum and urine creatinine were measured using the Abbot Creatinine Kit on the Abbot Architect Analyser, which utilises the Jaffe assay to measure creatinine. The lab reported coefficient of variation (CV) for a creatinine level of 73 micromol/L is 7%, and for a creatinine level of 534 micromol/L the CV is 2.8%.

Estimated glomerular filtration rates (eGFRs) were derived from the following formulas:

24 h urine creatinine clearance equation

$$\text{eGFR} = [\text{urine creatinine} \times 24\,\text{h urine volume}] \div \text{serum creatinine}$$

Nanra equation

$$\text{eGFR} = (140 - \text{age}) \times (\text{height})^2 \times (0.02588/\text{serum creatinine})$$

CKD-EPI equation

$$\text{eGFR} = 141 \times \min(\text{serum creatinine}/\text{kappa},\ 1)^{\text{alpha}} \times \max(^{\text{Serum creatinine}/\text{kappa},\ 1)-1.209} \times 0.993^{\text{Age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

$$\text{Kappa} = 0.7 \text{ if female, } 0.9 \text{ if male;}$$
$$\text{Alpha} = -0.329 \text{ if female, } -0.411 \text{ if male}$$

Normally distributed data were expressed as a mean with standard deviation. Non-normally distributed data were expressed as a median with an interquartile range. Based on measures of 24 h urine creatinine clearance in the healthy population, this study had a power of 80% to detect a difference in GFR of 15 ml/min with a significance level of 5%. All eGFR values were indexed for BSA in order to equate and compare units. The mean and standard deviation of creatinine clearance was calculated for each formula and compared with 24 h urine creatinine clearance. The agreed upon acceptable level of bias was ± 15 ml/min/1.73 m^2, consistent with other studies.[5]

Results

A total of 39 women provided 55 synchronous urine and serum creatinine samples (see Table 1). The majority of the women were Caucasian (92%), and no corrective factors were used for the other ethnicities when calculating their eGFR. Gestational ages ranged from 15 to 33 weeks, with the majority (83%) of women in their second trimester. One serum sample was excluded due to a lack of a synchronous urine sample. A second was excluded from the data analysis as an erroneous outlier. Both the CKD-EPI and Nanra equation had an acceptable level of bias, being ± 14.2 ml/min/1.73 m^2 and ± 13.4 ml/min/1.73 m^2 for these equations respectively (see Table 2).

Discussion

The Nanra and the CKD-EPI equations had poor agreement with the current gold standard, the 24 h urine creatinine clearance. Both serum creatinine-based eGFR formulas may not be accurate measures of renal function in pregnancy.

The *a priori* acceptance of ± 15 ml/min/1.73 m^2 bias comparing the validated 24 h urine creatinine clearance to a new eGFR measurement technique was achieved with the Nanra equation displaying a bias of -13.4 ml/min/1.73 m^2, similar to the bias of 6.8 ml/min found in comparing the 24 h creatinine clearance to inulin clearance.[5] The CKD-EPI equation also showed a promising result, with a bias of $+14.2$ ml/min/1.73 m^2. Despite this, the Bland-Altman plots show evidence of proportional error with each equation (see Figures 1 and 2), consistently over-estimating the eGFR at higher values, and under-estimating at low values.

Table 1. Patient characteristics and demographics.

Women (n)	39
24 h urine collection (n)	55
Age (years)	30 (±3.5)[a]
Ethnicity (n, %)	
Caucasian	36 (92)
South-East Asian	2 (5)
Central American	1 (3)
Gestational age (weeks)	22 (18.5–25)[b]
Number of urine collections	
First trimester (%)	0 (0)
Second trimester (%)	47 (85.5)
Third trimester (%)	8 (14.5)
Urine volume (ml)	2372 (±1079)[a]
Height (cm)	167 (±6.8)[a]
Weight (kg)	71 (±14.1)[a]
Body mass index (kg/m^2)	25 (±4.7)[a]
Systolic blood pressure (mmHg)	103 (±10.4)[a]
Diastolic blood pressure (mmHg)	62 (±7.4)[a]

[a]Standard deviation.
[b]Interquartile range.

Table 2. Bias and comparison of 24 h urine creatinine clearance to specified equations.

	Samples (n)	24 h creatinine clearance (ml/min/1.73 m^2)	eGFR (ml/min/1.73 m^2)	Bias	95% Limits of agreement
CKD-EPI	53	136.7 ($\pm$31.2)[a]	122.68 ($\pm$3.88)[a]	+14.2	−45.4 to 73.8
Nanra	53	136.7 ($\pm$31.2)[a]	150.86 ($\pm$14.35)[a]	−13.4	−78.7 to 51.9

CKD-EPI: chronic kidney disease epidemiology collaboration; eGFR: estimated glomerular filtration rate.
[a]Standard deviation.

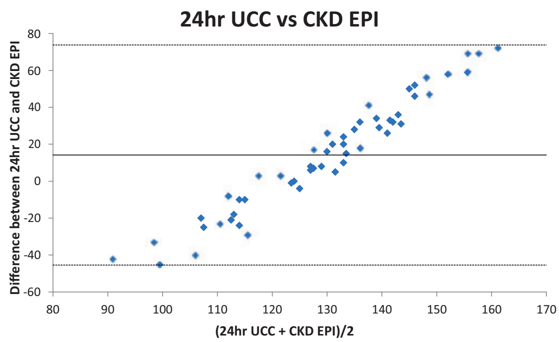

Figure 1. Bland-Altman plot comparing 24 h urine creatinine clearance (24 h UCC) to the CKD-EPI equation. (Solid lines indicate bias and dotted lines highlight 95% levels of agreement.)

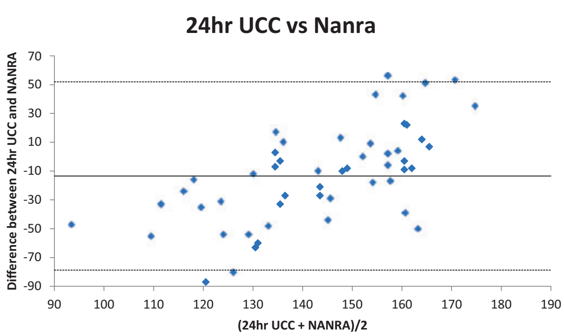

Figure 2. Bland-Altman plot comparing 24 h urine creatinine clearance (24 h UCC) to the Nanra equation. (Solid lines indicate bias and dotted lines highlight 95% levels of agreement.)

Previous studies have also shown that the CKD-EPI equation is not clinically useful in pregnancy.[10,11] Smith et al. measured a bias of 40 ml/min/1.73 m^2 when comparing the CKD-EPI equation against inulin clearance in 24 women during pregnancy. Our study showed less bias when comparing the CKD-EPI equation to 24 h urine creatinine clearance; however, our patient population had different gestational ages, being mostly in the second trimester, whereas Smith et al. measured their bias in the third trimester where the physiological changes affecting GFR is most pronounced. The Nanra equation was hypothesised to be potentially useful in pregnancy due to the exclusion of weight as a variable. Whilst this equation was shown to be a reasonable measure of eGFR in the renal transplant population, it had not been tested in the pregnant population. With the increase in weight during pregnancy not associated with increased muscle mass or increased creatinine production, it was thought this equation would yield more accurate results than the previously tested serum creatinine-based eGFR equations in the MDRD and CKD-EPI. However, this study has shown that the Nanra equation would also not be a clinically useful measure of eGFR during pregnancy. Future studies could consider an equation that factors in the staging of pregnancy, given the improvement in bias for the CKD-EPI equation in the second trimester compared to the bias in the third trimester as measured by Smith et al.[10] Following the trends in creatinine levels during pregnancy might be useful in formulating such an equation.[7]

A strength of this study was in its selection. The patient population were healthy without evidence of disease that could introduce variability into renal function analysis. This resulted in a degree of consistency throughout the population group and results could be generalised to the healthy pregnancy population. The methodology also made the data points easy to analyse, with each eGFR equation being compared the current validated technique and its level of concordance measured using a Bland-Altman plot. This allowed for minimal ambiguity in interpreting the results.

A weakness of this study was in the choice to compare the eGFR equations with 24 h urine creatinine clearance measurement with its own intrinsic degree of bias (bias 6.8 ± 34 ml/min compared to inulin; 95% limits of agreement between −60 and 74 ml/min, 95% CI −90.7 to 104.2).[5] The collection of 24 h urine presented a challenge, as shown by the large standard deviation in urine volume (Table 1). It has been shown to be an imprecise measure of urinary creatinine clearance due to variability in the rate of creatinine excretion, and measurement error is possible in pregnancy due to ureteric dilatation and incomplete emptying of the bladder.[13] The majority of women included were in the second trimester (83%), raising issues of external validity in women in other trimesters. A larger sample size where there is stratification based on gestational age would be ideal.

Conclusion

The search for an accurate estimation of GFR in pregnancy using a serum creatinine-based equation remains elusive. This study has shown that despite using an eGFR equation (Nanra) that would seemingly minimise the effect of physiological changes of pregnancy on GFR, it failed to show an acceptable agreement when compared to the current validated technique of measuring creatinine clearance from a 24 h urine sample. Moreover, the CKD-EPI equation also demonstrated a high degree of proportional error when compared to 24 h urine creatinine clearance. Further studies in this field are needed before the measurement of renal function in the pregnant population can be simplified.

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Supplemental material

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